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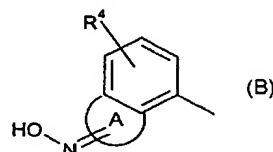
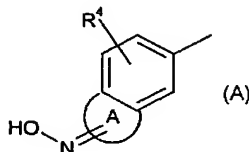
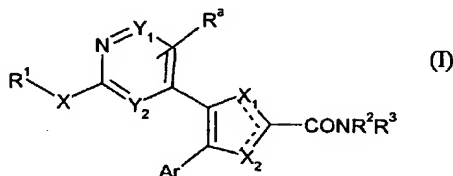
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(54) Title: IMIDAZOLE-2-CARBOXAMIDE DERIVATIVES AS RAF KINASE INHIBITORS



(57) Abstract: Compounds of formula (I): wherein X is O, CH₂, S or NH, or the moiety X-R¹ is hydrogen; Y₁ and Y₂ independently represent CH or N; R¹ is hydrogen, C₁₋₆alkyl, C₃₋₇cycloalkyl, aryl, arylC₁₋₆alkyl, heterocyclyl, heterocyclylC₁₋₆alkyl, heteroaryl, or heteroarylC₁₋₆alkyl, any of which except hydrogen may be optionally substituted; R² and R³ independently represent hydrogen, C₁₋₆alkyl, C₃₋₇cycloalkyl, aryl, arylC₁₋₆alkyl, heteroaryl, heterocyclyl, or heterocyclylC₁₋₆alkyl, or R² and R³ together with the nitrogen atom to which they are attached form a 4- to 10-membered monocyclic or bicyclic ring; Ar is a group of the formula a) or b), wherein A represents a fused 5- to 7-membered ring optionally containing up to two heteroatoms selected from O, S and NR⁵, wherein R⁵ is hydrogen or C₁₋₆alkyl, which ring is optionally substituted by up to 2 substituents selected from halo- gen, C₁₋₆alkyl, hydroxy, C₁₋₆alkoxy or keto; R^a and R⁴ are independently selected from hydrogen, halogen, C₁₋₆alkyl, aryl, arylC₁₋₆alkyl, C₁₋₆alkoxy, C₁₋₆alkoxyC₁₋₆alkyl, haloC₁₋₆alkyl, arylC₁₋₆alkoxy, hydroxy, nitro, cyano, azido, amino, mono- and di-N-C₁₋₆alkyl- lamino, acylamino, arylcarbonylamino, acyloxy, carboxy, carboxy salts, carboxy esters, carbamoyl, mono- and di-N-C₁₋₆alkylcar- bamoyl, C₁₋₆alkoxycarbonyl, aryloxy carbonyl, ureido, guanidino, C₁₋₆alkylguanidino, amidino, C₁₋₆alkylamidino, sulphonylamino, aminosulphonyl, C₁₋₆alkylthio, C₁₋₆alkyl sulphonyl or C₁₋₆alkylsulphonyl; and one of X₁ and X₂ is N and the other is NR⁶, wherein R⁶ is hydrogen, C₁₋₆alkyl, or arylC₁₋₆alkyl; or pharmaceutically acceptable salts thereof.

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IMIDAZOLE-2-CARBOXAMIDE DERIVATIVES AS RAF KINASE INHIBITORS

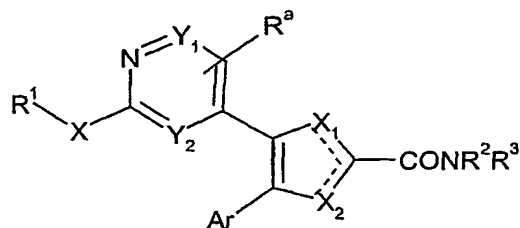
This invention relates to novel compounds and their use as pharmaceuticals particularly as Raf kinase inhibitors for the treatment of neurotraumatic diseases.

5 Raf protein kinases are key components of signal transduction pathways by which specific extracellular stimuli elicit precise cellular responses in mammalian cells. Activated cell surface receptors activate ras/rap proteins at the inner aspect of the plasmamembrane which in turn recruit and activate Raf proteins. Activated Raf proteins phosphorylate and activate the intracellular protein kinases MEK1 and MEK2. In turn, activated MEKs catalyse
10 phosphorylation and activation of p42/p44 mitogen-activated protein kinase (MAPK). A variety of cytoplasmic and nuclear substrates of activated MAPK are known which directly or indirectly contribute to the cellular response to environmental change. Three distinct genes have been identified in mammals that encode Raf proteins; A-Raf, B-Raf and C-Raf (also known as Raf-1) and isoformic variants that result from differential splicing of mRNA are
15 known.

Inhibitors of Raf kinases have been suggested for use in disruption of tumor cell growth and hence in the treatment of cancers, e.g. histiocytic lymphoma, lung adenocarcinoma, small cell lung cancer and pancreatic and breast carcinoma; and also in the treatment and/or prophylaxis of disorders associated with neuronal degeneration resulting
20 from ischemic events, including cerebral ischemia after cardiac arrest, stroke and multi-infarct dementia and also after cerebral ischemic events such as those resulting from head injury, surgery and/or during childbirth.

We have now found a group of novel compounds that are inhibitors of Raf kinases, in particular inhibitors of B-Raf kinase.

25 According to the invention there is provided a compound of formula (I):



(I)

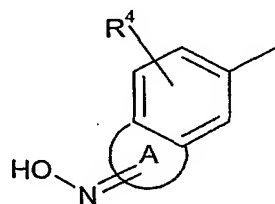
wherein

30 X is O, CH₂, S or NH, or the moiety X-R¹ is hydrogen;
Y₁ and Y₂ independently represent CH or N;

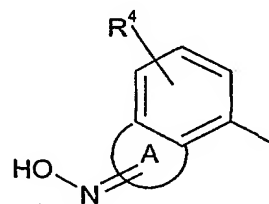
R^1 is hydrogen, C_{1-6} alkyl, C_{3-7} cycloalkyl, aryl, aryl C_{1-6} alkyl, heterocyclyl, heterocyclyl C_{1-6} alkyl, heteroaryl, or heteroaryl C_{1-6} alkyl any of which except hydrogen, may be optionally substituted;

R^2 and R^3 independently represent hydrogen, C_{1-6} alkyl, C_{3-7} cycloalkyl, aryl, aryl C_{1-6} alkyl, heteroaryl, heteroaryl C_{1-6} alkyl, heterocyclyl, or heterocyclyl C_{1-6} alkyl, or R^2 and R^3 together with the nitrogen atom to which they are attached form a 4- to 10-membered monocyclic or bicyclic ring;

Ar is a group of the formula a) or b):



a)



b)

wherein A represents a fused 5- to 7-membered ring optionally containing up to two heteroatoms selected from O, S and NR^5 , wherein R^5 is hydrogen or C_{1-6} alkyl, which ring is optionally substituted by up to 2 substituents selected from halogen, C_{1-6} alkyl, hydroxy, C_{1-6} alkoxy or keto;

R^a and R^4 are independently selected from hydrogen, halogen, C_{1-6} alkyl, aryl, aryl C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkoxy C_{1-6} alkyl, halo C_{1-6} alkyl, aryl C_{1-6} alkoxy, hydroxy, nitro, cyano, azido, amino, mono- and di- N - C_{1-6} alkylamino, acylamino, arylcarbonylamino, acyloxy, carboxy, carboxy salts, carboxy esters, carbamoyl, mono- and di- N - C_{1-6} alkylcarbamoyl, C_{1-6} alkoxycarbonyl, aryloxy carbonyl, ureido, guanidino, C_{1-6} alkylguanidino, amidino, C_{1-6} alkylamidino, sulphonylamino, aminosulphonyl, C_{1-6} alkylthio, C_{1-6} alkyl sulphinyl or C_{1-6} alkylsulphonyl; and

one of X_1 and X_2 is N and the other is NR^6 , wherein R^6 is hydrogen, C_{1-6} alkyl, or aryl C_{1-6} alkyl;

or a pharmaceutically acceptable salt thereof.

As used herein, the double bond indicated by the dotted lines of formula (I), represent the possible tautomeric ring forms of the compounds falling within the scope of this invention, the double bond being to the unsubstituted nitrogen atom.

The hydroxyimino moiety can be positioned on any of carbon atoms of the non-aromatic ring in groups a) and b).

The hydroxyimino moiety can exist as either the E or Z isomer or as a mixture of both.

Alkyl and alkenyl groups referred to herein, individually or as part of larger groups e.g. alkoxy, may be straight or branched groups containing up to six carbon atoms and are optionally substituted by one or more groups selected from the group consisting of aryl, heteroaryl, heterocyclyl, C₁₋₆alkoxy, C₁₋₆alkylthio, arylC₁₋₆alkoxy, arylC₁₋₆alkylthio, amino, mono- or di-C₁₋₆alkylamino, cycloalkyl, cycloalkenyl, carboxy and esters thereof, amide, sulphonamido, ureido, guanidino, C₁₋₆alkylguanidino, amidino, C₁₋₆alkylamidino, C₁₋₆acyloxy, azido, hydroxy, hydroxyimino and halogen.

Cycloalkyl and cycloalkenyl groups referred to herein include groups having from three to seven ring carbon atoms and are optionally substituted as described hereinabove for alkyl and alkenyl groups.

When used herein, the term "aryl" includes, unless otherwise defined, single and fused rings suitably containing from 4 to 7, preferably 5 or 6, ring atoms in each ring, which rings, may each be unsubstituted or substituted by, for example, up to three substituents.

Suitable aryl groups include phenyl and naphthyl such as 1-naphthyl or 2-naphthyl.

Optional substituents for alkyl, alkenyl, cycloalkyl and cycloalkenyl groups include aryl, heteroaryl, heterocyclyl, C₁₋₆alkoxy, C₁₋₆alkylthio, arylC₁₋₆alkoxy, arylC₁₋₆alkylthio, amino, mono- or di-C₁₋₆alkylamino, aminosulphonyl, cycloalkyl, cycloalkenyl, carboxy and esters thereof, amide, ureido, guanidino, C₁₋₆alkylguanidino, amidino, C₁₋₆alkylamidino, C₁₋₆acyloxy, hydroxy, and halogen or any combination thereof.

When used herein the term "heterocyclyl" includes, unless otherwise defined, non-aromatic, single and fused, rings suitably containing up to four heteroatoms in each ring, each of which is selected from O, N and S, which rings, may be unsubstituted or substituted by, for example, up to three substituents. Each heterocyclic ring suitably has from 4 to 7, preferably 5 or 6, ring atoms. A fused heterocyclic ring system may include carbocyclic rings and need include only one heterocyclic ring. Examples of heterocyclyl groups include pyrrolidine, piperidine, piperazine, morpholine, imidazolidine and pyrazolidine.

When used herein, the term "heteroaryl" includes, unless otherwise defined, mono- and bicyclic heteroaromatic ring systems comprising up to four, preferably 1 or 2, heteroatoms each selected from O, N and S. Each ring may have from 4 to 7, preferably 5 or 6, ring atoms. A bicyclic heteroaromatic ring system may include a carbocyclic ring. Examples of heteroaryl groups include pyrrole, quinoline, isoquinoline, pyridine, pyrimidine, oxazole, thiazole, thiadiazole, triazole, imidazole and benzimidazole.

Aryl, heterocyclyl and heteroaryl groups may be optionally substituted by preferably up to three substituents. Suitable substituents include halogen, C₁₋₆alkyl, aryl, aryl C₁₋₆alkyl, C₁₋₆alkoxy, C₁₋₆alkoxy C₁₋₆alkyl, halo C₁₋₆alkyl, arylC₁₋₆alkoxy, hydroxy, nitro, cyano, azido, amino, mono- and di-*N*-C₁₋₆alkylamino, acylamino,

5 arylcarbonylamino, acyloxy, carboxy, carboxy salts, carboxy esters, carbamoyl, mono- and di-*N*-C₁₋₆alkylcarbamoyl, C₁₋₆alkoxycarbonyl, aryloxy carbonyl, ureido, guanidino, C₁₋₆alkylguanidino, amidino, C₁₋₆alkylamidino, sulphonylamino, aminosulphonyl, C₁₋₆alkylthio, C₁₋₆alkylsulphanyl, C₁₋₆alkylsulphonyl, heterocyclyl, heteroaryl, heterocyclyl C₁₋₆alkyl, hydroxyimino-C₁₋₆alkyl and heteroaryl C₁₋₆alkyl, and combinations thereof.

10 Preferably the optional substituent contains a solubilising group; suitable solubilising moieties will be apparent to those skilled in the art and include hydroxy and amine groups. Even more preferably the optional substituent includes amino, mono- or di-C₁₋₆alkylamino, amine containing heterocyclyl, and hydroxy or any combination thereof.

15 X is preferably NH or X-R¹ is preferably hydrogen and when X is NH, R¹ is preferably hydrogen or C₁₋₆alkyl.

When Y₁ and Y₂ are CH, X-R¹ is preferably hydrogen.

When Y₂ is N, X-R¹ is preferably NH₂.

Preferrably R⁶ is hydrogen.

20 Most preferably X-R¹ is hydrogen

A is preferably a fused 5 membered ring optionally containing up to two heteroatoms selected from O, S and NR⁵, wherein R⁵ is hydrogen or C₁₋₆alkyl, which ring is optionally substituted by up to 2 substituents selected from halogen, C₁₋₆alkyl, hydroxy, C₁₋₆alkoxy or keto.

25 Even more preferably A is a fused 5 membered ring.

Preferably R² and R³ independently represent hydrogen, C₁₋₆alkyl, aryl, heteroarylC₁₋₆alkyl, heterocyclyl, heterocyclylC₁₋₆alkyl, any of which except hydrogen can be optionally substituted or R² and R³ together with the nitrogen atom to which they are attached form an optionally substituted 5 or 6 membered monocyclic or bicyclic ring for example piperidine.

30 The compounds of formula (I) preferably have a molecular weight of less than 800.

Preferred substituents for the group Ar include halo, hydroxy, hydroxy C₁₋₆alkyl, hydroxyimino-C₁₋₆alkyl and C₁₋₆alkoxy.

35 It will be understood that the invention includes pharmaceutically acceptable derivatives of compounds of formula (I) and that these are included within the scope of the invention.

Particular compounds according to the invention include those mentioned in the examples and their pharmaceutically acceptable salts. As used herein "pharmaceutically

acceptable derivatives" includes any pharmaceutically acceptable salt, ester or salt of such ester of a compound of formula (I) which, upon administration to the recipient, is capable of providing (directly or indirectly) a compound of formula (I) or an active metabolite or residue thereof.

5 It will be appreciated that for use in medicine the salts of the compounds of formula (I) should be pharmaceutically acceptable. Suitable pharmaceutically acceptable salts will be apparent to those skilled in the art and include those described in *J. Pharm. Sci.*, 1977, 66, 1-19, such as acid addition salts formed with inorganic acids e.g. hydrochloric, hydrobromic, sulfuric, nitric or phosphoric acid; and organic acids e.g. 10 succinic, maleic, acetic, fumaric, citric, tartaric, benzoic, p-toluenesulfonic, methanesulfonic or naphthalenesulfonic acid. Other salts e.g. oxalates, may be used, for example in the isolation of compounds of formula (I) and are included within the scope of this invention.

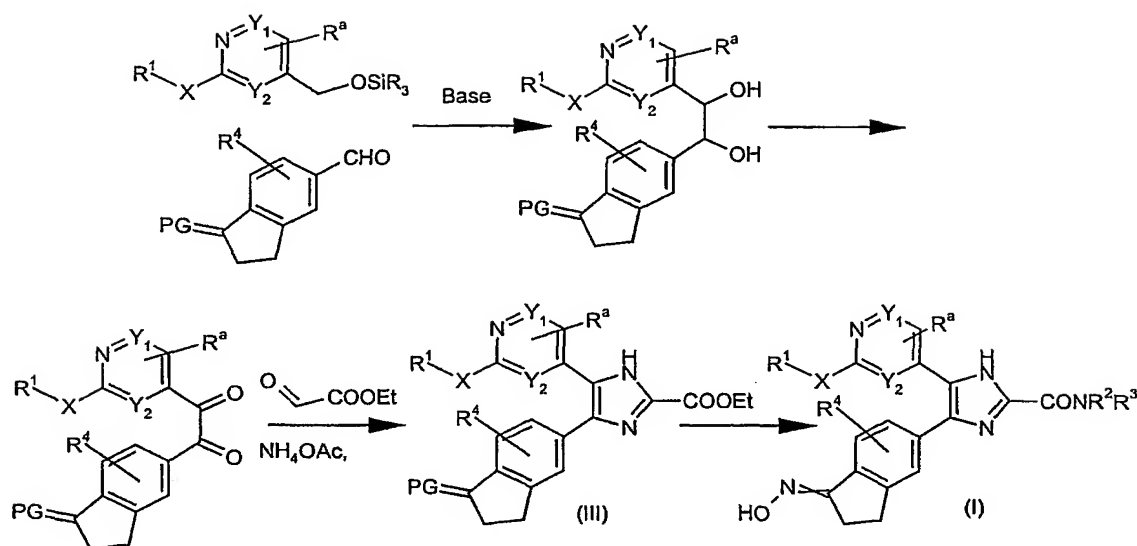
The compounds of this invention may be in crystalline or non-crystalline form, 15 and, if crystalline, may optionally be hydrated or solvated. This invention includes within its scope stoichiometric hydrates as well as compounds containing variable amounts of water.

The invention extends to all isomeric forms including stereoisomers and geometric isomers of the compounds of formula (I) including enantiomers and mixtures 20 thereof e.g. racemates. The different isomeric forms may be separated or resolved one from the other by conventional methods, or any given isomer may be obtained by conventional synthetic methods or by stereospecific or asymmetric syntheses.

Since the compounds of formula (I) are intended for use in pharmaceutical compositions it will readily be understood that they are each preferably provided in 25 substantially pure form, for example at least 60% pure, more suitably at least 75% pure and preferably at least 85%, especially at least 98% pure (% are on a weight for weight basis). Impure preparations of the compounds may be used for preparing the more pure forms used in the pharmaceutical compositions.

Compounds of Formula (I) are imidazole derivatives which may be readily 30 prepared using procedures well-known to those skilled in the art, and described in, for instance, *Comprehensive Heterocyclic Chemistry*, Editors Katritzky and Rees, Pergamon Press, 1984, 5, 457-497, from starting materials which are either commercially available or can be prepared from such by analogy with well-known processes. A key step in many such syntheses is the formation of the central imidazole nucleus.

35



Preferred methods for preparing compounds of this invention are as outlined in the above scheme. α -Diketones are prepared by condensation of the anion of, for example, a 4-substituted pyridine derivative ($Y_1=Y_2=CH$, $R^1-X=H$ and $R^4=R^a=H$) with a suitably protected fused bicyclic arylaldehyde (e.g. 1-methoxyimino-indan-5-carboxaldehyde) followed by oxidation of the intermediate product. Stirring the diketone with an aldehyde, such as glyoxylic acid ethyl ester, and ammonium acetate in a mixture of methanol and methyl-*tert*-butyl ether allows access to the imidazole nucleus, by analogy to the method described in patent WO 98/56788. Thereafter, the ethyl ester may be converted into an amide using conventional amide bond forming procedures (such procedures are well known in the art and are described in, for instance, P.D. Bailey, I.D. Collier and K.M. Morgan in *Comprehensive Organic Functional Group Transformation*, Vol. 5, ed. C.J. Moody, p.257, Elsevier Scientific, Oxford, 1995.) and the group PG converted into an hydroxyimono group ($HO-N=$).

Non-selective alkylation of the imidazole nitrogen (using one of the procedures outlined in N. J. Liverton et al; *J. Med. Chem.*, 1999, **42**, 2180-2190) with a compound of formula $L-R^4$ wherein L is a leaving group, e.g. halo, sulfonate or triflate, will yield both isomers of the compounds where X_1 or X_2 is NR^6 in which R^6 is other than hydrogen, the isomers can be separated by chromatographic methods.

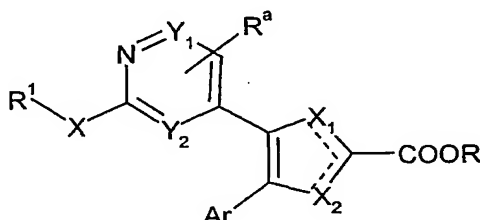
During the synthesis of the compounds of formula (I) labile functional groups in the intermediate compounds, e.g. hydroxy, carboxy and amino groups, may be protected. A comprehensive discussion of the ways in which various labile functional groups groups may be protected and methods for cleaving the resulting protected derivatives is given in for example *Protective Groups in Organic Chemistry*, T.W. Greene and P.G.M. Wuts, (Wiley-Interscience, New York, 2nd edition, 1991).

The compounds of formula (I) may be prepared singly or as compound libraries comprising at least 2, for example 5 to 1,000 compounds, and more preferably 10 to 100 compounds of formula (I). Libraries of compounds of formula (I) may be prepared by a combinatorial 'split and mix' approach or by multiple parallel synthesis using either solution phase or solid phase chemistry, by procedures known to those skilled in the art.

Thus according to a further aspect of the invention there is provided a compound library comprising at least 2 compounds of formula (I), or pharmaceutically acceptable salts thereof.

Pharmaceutically acceptable salts may be prepared conventionally by reaction with the appropriate acid or acid derivative.

The novel carboxylic esters and the corresponding acids of formula (II) and (III) which are used as intermediates in the synthesis of the compounds of formula (I) also form part of the present invention:



(II)

wherein X, Y₁, Y₂, R¹, R^a, Ar, X₁ and X₂ are as defined for formula (I) and R is hydrogen, C₁-₆alkyl or arylC₁₋₆alkyl.

As indicated above the compounds of formula (I) and their pharmaceutically acceptable derivatives are useful for the treatment and/or prophylaxis of disorders in which Raf kinases, in particular B-Raf kinase, are implicated.

According to a further aspect of the invention there is provided the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof as an inhibitor of B-Raf kinase.

As indicated above the compounds of formula (I) and their pharmaceutically acceptable derivatives are useful the treatment and/or prophylaxis of disorders associated with neuronal degeneration resulting from ischemic events.

According to a futher aspect of the invention there is provided a method of treatment or prophylaxis of a neurotraumatic disease, in a mammal in need thereof, which comprises administering to said mammal an effective amount of a compound of formula (I) or a pharmaceutically acceptable derivative thereof.

According to a futher aspect of the invention there is provided the use of a compound of formula (I) or a pharmaceutically acceptable derivative thereof in the manufacture of a medicament for the prophylactic or therapeutic treatment of any disease state in a human, or other mammal, which is exacerbated or caused by a neurotraumatic event.

Neurotraumatic diseases/events as defined herein include both open or penetrating head trauma, such as caused by surgery, or a closed head trauma injury, such as caused by an injury to the head region. Also included within this definition is ischemic stroke, particularly to the brain area, transient ischemic attacks following coronary by-pass and cognitive decline following other transient ischemic conditions.

Ischemic stroke may be defined as a focal neurologic disorder that results from insufficient blood supply to a particular brain area, usually as a consequence of an embolus, thrombi, or local atheromatous closure of the blood vessel. Roles for stress stimuli (such as anoxia), redox injury, excessive neuronal excitatory stimulation and inflammatory cytokines in this area has been emerging and the present invention provides a means for the potential treatment of these injuries. Relatively little treatment, for an acute injury such as these has been available.

The compounds of the invention may also be used in the treatment or prophylaxis of cancers.

In order to use the compounds of formula (I) in therapy, they will normally be formulated into a pharmaceutical composition in accordance with standard pharmaceutical practice.

According to a further aspect of the invention there is provided a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable derivative thereof and a pharmaceutically acceptable carrier.

The compounds of formula (I) may conveniently be administered by any of the routes conventionally used for drug administration, for instance, parenterally, orally, topically or by inhalation. The compounds of formula (I) may be administered in conventional dosage forms prepared by combining it with standard pharmaceutical carriers according to conventional procedures. The compounds of formula (I) may also be administered in conventional dosages in combination with a known, second therapeutically active compound. These procedures may involve mixing, granulating and compressing or dissolving the ingredients as appropriate to the desired preparation. It will be appreciated that the form and character of the pharmaceutically acceptable carrier is dictated by the amount of compound of formula (I) with which it is to be combined, the route of administration and other well-known variables. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The pharmaceutical carrier employed may be, for example, either a solid or liquid. Exemplary of solid carriers are lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, stearic acid and the like. Exemplary of liquid carriers are syrup, peanut oil, olive oil, water and the like. Similarly, the carrier or diluent may include time delay

material well known to the art, such as glyceryl mono-stearate or glyceryl distearate alone or with a wax.

5 A wide variety of pharmaceutical forms can be employed. Thus, if a solid carrier is used, the preparation can be tableted, placed in a hard gelatin capsule in powder or pellet form or in the form of a troche or lozenge. The amount of solid carrier will vary widely but preferably will be from about 25mg to about 1g. When a liquid carrier is used, the preparation will be in the form of a syrup, emulsion, soft gelatin capsule, sterile injectable liquid such as an ampoule or nonaqueous liquid suspension.

10 The compounds of formula (I) are preferably administered parenterally, that is by intravenous, intramuscular, subcutaneous intranasal, intrarectal, intravaginal or intraperitoneal administration. The intravenous form of parenteral administration is generally preferred. The compounds may be administered as a bolus or continuous infusion e.g. over 3 days. Appropriate dosage forms for such administration may be prepared by conventional techniques.

15 The compounds of formula (I) may also be administered orally. Appropriate dosage forms for such administration may be prepared by conventional techniques.

The compounds of formula (I) may also be administered by inhalation, that is by intranasal and oral inhalation administration. Appropriate dosage forms for such administration, such as aerosol formulations, may be prepared by conventional techniques.

20 The compounds of formula (I) may also be administered topically, that is by non-systemic administration. This includes the application of the inhibitors externally to the epidermis or the buccal cavity and the instillation of such a compound into the ear, eye and nose, such that the compound does not significantly enter the blood stream.

For all methods of use disclosed herein the daily oral dosage regimen will preferably
25 be from about 0.1 to about 80 mg/kg of total body weight, preferably from about 0.2 to 30 mg/kg, more preferably from about 0.5mg to 15mg. The daily parenteral dosage regimen about 0.1 to about 80 mg/kg of total body weight, preferably from about 0.2 to about 30 mg/kg, and more preferably from about 0.5mg to 15mg/kg. The daily topical dosage regimen will preferably be from 0.1 mg to 150mg, administered one to four, preferably two or three
30 times daily. The daily inhalation dosage regimen will preferably be from about 0.01 mg/kg to about 1 mg/kg per day. It will also be recognized by one of skill in the art that the optimal quantity and spacing of individual dosages of the inhibitors will be determined by the nature and extent of the condition being treated, the form, route and site of administration, and the particular patient being treated, and that such optimums can be determined by conventional
35 techniques. It will also be appreciated by one of skill in the art that the optimal course of treatment, i.e., the number of doses of the inhibitors given per day for a defined number of days, can be ascertained by those skilled in the art using conventional course of treatment

determination tests. In the case of pharmaceutically acceptable salts the above figures are calculated as the parent compound of formula (I).

No toxicological effects are indicated/expected when a compound of formula (I) is administered in the above mentioned dosage range.

5 All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

10 The following Examples illustrate the preparation of pharmacologically active compounds of the invention and the following Descriptions illustrate the preparation of intermediates used in the preparation of these compounds.

Abbreviations used herein are as follows;

15 THF means tetrahydrofuran.
DMF means N,N-Dimethylformamide.
LDA means lithium diisopropylamide.
TBAF means tetrabutylammonium fluoride.
DMSO means methyl sulfoxide.

20

Description 1: 4-(1-Oxo-indan-5-yl)-5-pyridin-4-yl-1H-imidazole-2-carboxylic acid

Step 1. 5-Bromo-indan-1-one O-methyl-oxime

To a solution of 5-bromo-indanone (100g, 0.474mol) in ethanol (650ml) under argon was added methoxylamine hydrochloride (198g, 2.38mol) and pyridine (125ml). The mixture
25 was refluxed for 2.5 hours, cooled to room temperature and poured into saturated aqueous sodium hydrogen carbonate solution. The mixture was then extracted with ethyl acetate and the organic phase dried (Na₂SO₄) and then concentrated *in vacuo*. The crude material was recrystallised from isopropanol to furnish the title compound, (110g, 97%), as a brown solid; ¹H NMR (CDCl₃) 7.52 (1H, d, J 8.3Hz), 7.43 (1H, d, J 1Hz), 7.35 (1H,
30 dd, J 8.3, 1Hz), 3.97 (3H, s), 2.99 (2H, m), 2.85 (2H, m).

Step 2. 1-Methoxyimino-indan-5-carbaldehyde

To a solution of the product of Step 1 (112g, 0.46mol) in THF (1500ml) at -60°C under argon, was added n-BuLi (325ml, 0.52mol) over 1 hour. After stirring at -60°C for 1 hour a solution of DMF (39.7ml) in THF (50ml) was added dropwise over 1 hour. The
35 reaction was stirred at -60°C for 1 hour before being allowed to warm to room temperature. After 1 hour the reaction was quenched with saturated aqueous sodium hydrogen carbonate solution and extracted into ethyl acetate. The organic phase was then

dried (Na_2SO_4), concentrated *in vacuo* and the residue purified by silica gel chromatography, to give the title compound (57g, 65%) as a yellow solid; ^1H NMR (CDCl_3) 10.0 (1H, s), 7.83-7.73 (3H, m), 4.02 (3H, s), 3.10 (2H, m), 2.92 (2H, m).

Step 3. 5-(1,2-Dihydroxy-2-pyridin-4-yl-ethyl)-indan-1-one-O-methyl-oxime

- 5 To a solution of 4-(tert-butyl-dimethyl-silyloxymethyl)-pyridine [T.F. Gallagher *et al*, *Bioorg. Med. Chem.*, 1997, 5, 49] (71.5g, 0.32mol) in THF (800ml) at -50°C under argon was added LDA (162ml, 2M in heptane/THF/ethylbenzene, 0.324mol) over 1 hour. The mixture was stirred at -40°C for a further 1 hour before a solution of the product of Step 2 (55g, 0.29mol) in THF (600ml) was added over 1 hour. The reaction was then allowed
- 10 to warm to room temperature overnight before being quenched by the addition of saturated aqueous sodium hydrogen carbonate solution and then extracted into ethyl acetate. The organic phase was dried (Na_2SO_4) and concentrated *in vacuo* to give a brown oil (125g).

- The oil was then dissolved in THF (1500ml), treated with TBAF (356ml, 0.356mol) and
- 15 stirred for 1 hour. The reaction mixture was then evaporated and the residue partitioned between water and ethyl acetate. The organic phase was then dried (Na_2SO_4) and concentrated to give the title compound (57g, 64%) as a pale yellow solid which was used without further purification. ^1H NMR (CDCl_3) 8.38 (2H, m), 7.57 (1H, m), 7.12-6.99 (4H, m), 4.88 (1H, m), 4.66 (1H, m), 3.96 (3H, s), 2.93 (2H, m), 2.85 (2H, m).

Step 4. 1-(1-Methoxyimino-indan-5-yl)-2-pyridin-4-yl-ethane-1,2-dione

- To a mixture of DMSO (43ml, 0.56mol) and dichloromethane (800ml) at -70°C under argon, was added oxalyl chloride (43.2g) and then a solution of the product of Step 3 (55g, 0.185mol) in a mixture of dichloromethane/DMSO (1000ml/60ml) over 2 hours at -60°C . After stirring for 2 hours at -60°C , triethylamine (154ml) was added dropwise
- 25 and the mixture then allowed to warm to room temperature overnight. The reaction mixture was then quenched with water, the organic phase separated then washed with water, dried (Na_2SO_4) and concentrated to yield the title compound (51g, 94%) as a yellow solid. ^1H NMR (CDCl_3) 8.87 (2H, d), 7.89-7.77 (5H, m), 4.03 (3H, s), 3.09 (2H, m), 2.93 (2H, m).

Step 5. 4-(1-Methoxyimino-indan-5-yl)-5-pyridin-4-yl-1H-imidazole-2-carboxylic acid ethyl ester

- A mixture of the product of Step 4 (4.3g, 15mmol) and glyoxylic acid ethyl ester (50% solution in toluene, 6ml, 30mmol) in *tert*-butyl-methyl ether (150ml) at 5°C was treated with a solution of ammonium acetate (11.2g, 145mmol) in methanol (50ml). After
- 35 stirring at room temperature for 2 hours the solution was evaporated *in vacuo* and the residue was partitioned between chloroform and saturated sodium hydrogen carbonate solution. The organic layer was separated, washed with water and brine, dried (MgSO_4),

filtered and concentrated at reduced pressure. Purification of the residue by chromatography on silica gel eluting with 5% methanol in chloroform gave the title compound as a yellow solid (1.0g, 18%); MS(AP+) m/e 377 [M+H]⁺.

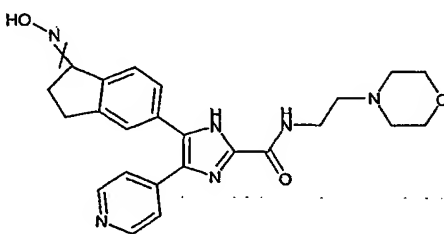
5 **Step 6. 4-(1-Oxo-indan-5-yl)-5-pyridin-4-yl-1H-imidazole-2-carboxylic acid ethyl ester dihydrochloride salt**

A mixture of the product of Step 5 (1.0g, 2.7mmol) and 5M HCl (15ml) in dioxane (30ml) / acetone (30ml) was heated to 100°C for 3 hour. The mixture was cooled to room temperature and the solvent evaporated *in vacuo*. The residue was co-evaporated with acetone (2x20ml) and ethanol / acetone (1:1, 20ml) to give the title compound (1.0g, 88%); MS(ES⁻) m/e 346 [M-H]⁻.

10 **Step 7. 4-(1-Oxo-indan-5-yl)-5-pyridin-4-yl-1H-imidazole-2-carboxylic acid**

A solution of the product of Step 6 (1.0g, 2.4mmol) in ethanol (10ml) containing, 10% aqueous sodium hydroxide solution (10ml) was heated at 50°C overnight. On cooling, the solvent was removed in vacuo, the residue dissolved in water and the pH adjusted to 6 with glacial acetic acid and the solvent re-evaporated. The residue was suspended in water (50ml) and the solid was collected, washed with water and dried over phosphorous pentoxide to give the crude title compound as an off-white solid (0.7g); MS(AP⁺) m/e 318 [M-H]⁻.

20 **Example 1: 4-(1-Hydroxyimino-indan-5-yl)-5-pyridin-4-yl-1H-imidazole-2-carboxylic acid (2-morpholin-4-yl-ethyl)-amide**



25 **Step 1. 4-(1-Oxo-indan-5-yl)-5-pyridin-4-yl-1H-imidazole-2-carboxylic acid (2-morpholin-4-yl-ethyl)-amide**

A mixture of the product of Description 1 (105mg, 0.33mmol), 1-hydroxybenzotriazole (68mg, 0.5mmol) and N-cyclohexylcarbodiimide-N'-methyl polystyrene (500mg, 0.66mmol, resin loading 1.32mmol/g) in DMF (2ml) was stirred at room temperature for 30 minutes. A solution of 2-morpholin-4-yl-ethylamine (43mg, 0.33mmol) in dichloromethane (0.5ml) was added and the mixture stirred at room temperature for 24 hours. The mixture was filtered through an SCX cation exchange resin column eluting with methanol followed by 10% 0.880 ammonia solution in methanol to elute the

product. Following concentration, the residue was purified by silica gel chromatography eluting with a 1:9:90 mixture of 0.880 ammonia solution: methanol: chloroform gave the title compound (65mg, 46%) as a yellow solid; MS(AP+) m/e 432 [M+H]⁺.

Step 2. 4-(1-Hydroxyimino-indan-5-yl)-5-pyridin-4-yl-1H-imidazole-2-carboxylic acid (2-morpholin-4-yl-ethyl)-amide

A solution of the product of Step 1 (65mg, 0.15mmol) in ethanol (4ml) and aqueous hydroxylamine (1ml, 50% in water) was heated under reflux for 1 hour. After cooling to room temperature, the solution was concentrated *in vacuo* and the residue co-evaporated with ethanol (3x10ml). Purification of the residue by silica gel chromatography eluting with a 1:9:90 mixture of 0.88 ammonia solution: methanol: chloroform gave the title compound (50mg, 75%) as a yellow solid; MS(AP+) m/e 447 [M+H]⁺.

The following examples were prepared from by the general two-step method described in Example 1.

Example		Amine	Characterisation
2	5-(2-{1-[4-(2-Methoxy-ethyl)-piperazin-1-yl]-methanoyl}-5-pyridin-4-yl-1H-imidazol-4-yl)-indan-1-one oxime	1-(2-Methoxy-ethyl)-piperazine	MS(AP+) m/e 461 [M+H] ⁺
3	4-(1-Hydroxyimino-indan-5-yl)-5-pyridin-4-yl-1H-imidazol-2-carboxylic acid methyl-(1-methyl-piperidin-4-yl)-amide	Methyl-(1-methyl-piperidin-4-yl)-amine	MS(AP+) m/e 445 [M+H] ⁺
4	5-{2-[1-(4-Cyclohexyl-piperazin-1-yl)-methanoyl]-5-pyridin-4-yl-1H-imidazol-4-yl}-indan-1-one oxime	1-Cyclohexyl-piperazine	MS(AP+) m/e 485 [M+H] ⁺
5	5-[2-(1-[1,4']-Bipiperidiny-1'-yl-methanoyl)-5-pyridin-4-yl-1H-imidazol-4-yl]-indan-1-one oxime	4-Piperidino-piperidine	MS(AP+) m/e 485 [M+H] ⁺
6	5-(2-{1-[4-(4-Chloro-benzyl)-piperazin-1-yl]-methanoyl}-5-pyridin-4-yl-1H-imidazol-4-yl)-indan-1-one oxime	1-(4-Chloro-benzyl)-piperazine	MS(AP+) m/e 453 [M+H] ⁺
7	4-(1-Hydroxyimino-indan-5-yl)-5-pyridin-4-yl-1H-imidazol-2-carboxylic acid methyl-(3-dimethylaminomethyl-phenyl)-amide	3-Dimethylamino-methyl-phenylamine	MS(AP+) m/e 467 [M+H] ⁺
8	4-(1-Hydroxyimino-indan-5-yl)-5-	[4-(2-	MS(AP+) m/e

	pyridin-4-yl-1H-imidazol-2-carboxylic acid [4-(2-diisopropylamino-ethoxy)-3-methoxy-phenyl]-methyl-amide	Diisopropyl-amino-ethoxy)-3-methoxy-phenyl]-methyl-amine	597 [M+H] ⁺
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It is to be understood that the present invention covers all combinations of particular and preferred subgroups described hereinabove.

5

BIOLOGICAL EXAMPLES

The activity of compounds of formula (I) as B-Raf inhibitors may be determined by the following *in vitro* assay:

10 Fluorescence anisotropy kinase binding assay

The kinase enzyme, fluorescent ligand and a variable concentration of test compound are incubated together to reach thermodynamic equilibrium under conditions such that in the absence of test compound the fluorescent ligand is significantly (>50%) enzyme bound and in the presence of a sufficient concentration (>10x K_i) of a potent inhibitor the anisotropy of the unbound fluorescent ligand is measurably different from the bound value.

15

The concentration of kinase enzyme should preferably be $\geq 1 \times K_f$. The concentration of fluorescent ligand required will depend on the instrumentation used, and the fluorescent and physicochemical properties. The concentration used must be lower than the concentration of kinase enzyme, and preferably less than half the kinase enzyme concentration. A typical protocol is:

20

All compounds dissolved in Buffer of comparison 50 mM HEPES, pharmaceutical 7.5, 1mM CHAPS, 10 mM MgCl₂.

B-Raf Enzyme concentration: 1 nM

Fluorescent ligand concentration: 0.5 nM

25

Test compound concentration: 0.5 nM – 100 uM

Components incubated in 10 ul final volume in LJL HE 384 type B black microtitre plate until equilibrium reached (Over 3 h, up to 30 h)

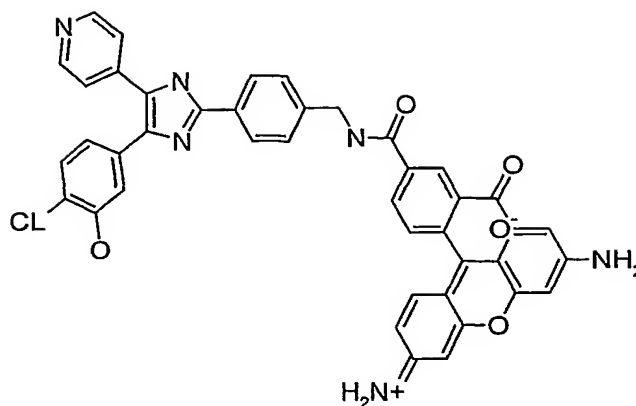
Fluorescence anisotropy read LJL Acquest.

Definitions: K_i = dissociation constant for inhibitor binding

30

K_f = dissociation constant for fluorescent ligand binding

The fluorescent ligand is the following compound:



which is derived from 5-[2-(4-aminomethylphenyl)-5-pyridin-4-yl-1H-imidazol-4-yl]-
 5 2-chlorophenol and rhodamine green.

Compounds of the invention have a K_d of less than 1 μ M.

Raf Kinase assay

10 Activity of human recombinant B-Raf protein was assessed in vitro by assay of the incorporation of radiolabelled phosphate to recombinant MAP kinase (MEK), a known physiologic substrate of B-Raf. Catalytically active human recombinant B-Raf protein was obtained by purification from sf9 insect cells infected with a human B-Raf recombinant baculovirus expression vector. To ensure that all substrate phosphorylation
 15 resulted from B-Raf activity, a catalytically inactive form of MEK was utilised. This protein was purified from bacterial cells expression mutant inactive MEK as a fusion protein with glutathione-S-transferase (GST-kdMEK).

Method: Standard assay conditions of B-Raf catalytic activity utilised 3 μ g of GST-kdMEK, 10 μ M ATP and 2 μ Ci 33 P-ATP, 50mM MOPS, 0.1mM EDTA, 0.1M sucrose,
 20 10mM $MgCl_2$ plus 0.1% dimethylsulphoxide (containing compound where appropriate) in a total reaction volume of 30 μ l. Reactions were incubated at 25°C for 90 minutes and reactions terminated by addition of EDTA to a final concentration of 50 μ M. 10 μ l of reaction was spotted to P30 phosphocellulose paper and air dried. Following four washes in ice cold 10% trichloroacetic acid, 0.5% phosphoric acid, papers were air dried prior to
 25 addition of liquid scintillant and measurement of radioactivity in a scintillation counter.

Results: The compounds of the examples were found to be effective in inhibiting B-Raf mediated phosphorylation of GST-kdMEK substrate having IC_{50} 's of < 3 μ M.

The activity of compounds as Raf inhibitors may also be determined by the assays described in WO 99/10325; McDonald, O.B., Chen, W.J., Ellis, B., Hoffman, C., Overton, L., Rink, M., Smith, A., Marshall, C.J. and Wood, E.R. (1999) A scintillation proximity assay for the Raf/MEK/ERK kinase cascade: high throughput screening and
5 identification of selective enzyme inhibitors, *Anal. Biochem.* 268: 318-329 and AACR meeting New Orleans 1998 Poster 3793.

The neuroprotective properties of B-Raf inhibitors may be determined by the following *in vitro* assay:

10 **Neuroprotective properties of B-Raf inhibitors in rat hippocampal slice cultures**

Organotypic cultures provide an intermediate between dissociated neuronal cell cultures and *in-vivo* models of oxygen and glucose deprivation (OGD). The majority of glial-neuronal interactions and neuronal circuitry are maintained in cultured hippocampal slices, so facilitating investigation of the patterns of death among differing cell types in a
15 model that resembles the *in vivo* situation. These cultures allow the study of delayed cellular damage and death 24 hours, or more, post-insult and permit assessment of the consequences of long-term alterations in culture conditions. A number of laboratories have reported delayed neuronal damage in response to OGD in organotypic cultures of the hippocampus (Vornov *et al.*, *Stroke*, 1994, 25, 57-465; Newell *et al.*, *Brain Res.*,
20 1995, 676, 38-44). Several classes of compounds have been shown to protect in this model, including EAA antagonists (Strasser *et al.*, *Brain Res.*, 1995, 687, 167-174), Na channel blockers (Tasker *et al.*, *J. Neurosci.*, 1992, 12, 98-4308) and Ca channel blockers (Pringle *et al.*, *Stroke*, 1996, 7, 2124-2130). To date, relatively little is known of the roles of intracellular kinase mediated signalling pathways in neuronal cell death in this model.
25 **Method:** Organotypic hippocampal slice cultures were prepared using the method of Stoppini *et al.*, *J. Neurosci. Methods*, 1995, 37, 173-182. Briefly, 400 micron sections prepared from hippocampi of 7-8 day postnatal Sprague Dawley rats are cultured on semiporous membranes for 9-12 days. OGD is then induced by incubation in serum and glucose-free medium in an anaerobic chamber for 45 minutes. Cultures are then returned
30 to the air / CO₂ incubator for 23 hours before analysis. Propidium iodide (PI) is used as an indicator of cell death. PI is non toxic to neurones and has been used in many studies to ascertain cell viability. In damaged neurons PI enters and binds to nucleic acids. Bound PI shows increased emission at 635nm when excited at 540nm. One PI fluorescence image and one white light image are taken and the proportion of cell death
35 analysed. The area of region CA1 is defined from the white light image and superimposed over the PI image. The PI signal is thresholded and area of PI damage expressed as a percentage of the CA1 area. Correlation between PI fluorescence and

histologically confirmed cell death has been validated previously by Nissl-staining using cresyl fast violet (Newell *et al.*, *J. Neurosci.*, 1995, 15, 7702-7711).

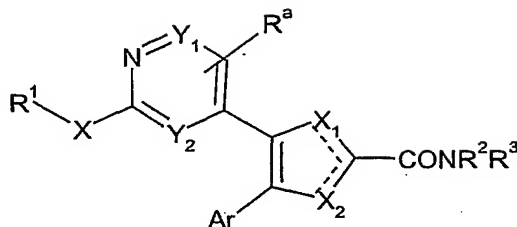
It is to be understood that the present invention covers all combination of particular and preferred groups described herein above.

- 5 Throughout the specification and the claims which follow, unless the context requires otherwise, the word 'comprise', and variations such as 'comprises' and 'comprising', will be understood to imply the inclusion of a stated integer or step or group of integers but not to the exclusion of any other integer or step or group of integers or steps.

- 10 The application of which this description and claims forms part may be used as a basis for priority in respect of any subsequent application. The claims of such subsequent application may be directed to any feature or combination of features described herein. They may take the form of composition, process, or use claims and may include by way of example and without limitation the following claims.

Claims:

1. A compound of formula (I):



5

(I)

wherein

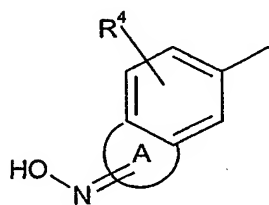
X is O, CH₂, S or NH, or the moiety X-R¹ is hydrogen;

Y₁ and Y₂ independently represent CH or N;

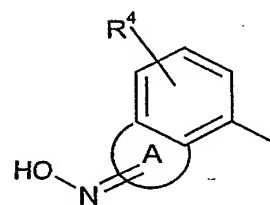
10 R¹ is hydrogen, C₁₋₆alkyl, C₃₋₇cycloalkyl, aryl, arylC₁₋₆alkyl, heterocyclyl, heterocyclylC₁₋₆alkyl, heteroaryl, or heteroarylC₁₋₆alkyl, any of which except hydrogen may be optionally substituted;

R² and R³ independently represent hydrogen, C₁₋₆alkyl, C₃₋₇cycloalkyl, aryl, arylC₁₋₆alkyl, heteroaryl, heteroarylC₁₋₆alkyl, heterocyclyl, or heterocyclylC₁₋₆alkyl, or
 15 R² and R³ together with the nitrogen atom to which they are attached form a 4- to 10-membered monocyclic or bicyclic ring;

Ar is a group of the formula a) or b):



a)



b)

20

wherein A represents a fused 5- to 7-membered ring optionally containing up to two heteroatoms selected from O, S and NR⁵, wherein R⁵ is hydrogen or C₁₋₆alkyl, which
 25 ring is optionally substituted by up to 2 substituents selected from halogen, C₁₋₆alkyl, hydroxy, C₁₋₆alkoxy or keto;

R^a and R⁴ are independently selected from hydrogen, halogen, C₁₋₆alkyl, aryl, arylC₁₋₆alkyl, C₁₋₆alkoxy, C₁₋₆alkoxyC₁₋₆alkyl, haloC₁₋₆alkyl, arylC₁₋₆alkoxy, hydroxy, nitro, cyano, azido, amino, mono- and di-N-C₁₋₆alkylamino, acylamino,

arylcarbonylamino, acyloxy, carboxy, carboxy salts, carboxy esters, carbamoyl, mono- and di-*N*-C₁₋₆alkylcarbamoyl, C₁₋₆alkoxycarbonyl, aryloxycarbonyl, ureido, guanidino, C₁₋₆alkylguanidino, amidino, C₁₋₆alkylamidino, sulphonylamino, aminosulphonyl, C₁₋₆alkylthio, C₁₋₆alkyl sulphinyl or C₁₋₆alkylsulphonyl; and

- 5 one of X₁ and X₂ is N and the other is NR⁶, wherein R⁶ is hydrogen, C₁₋₆alkyl, or arylC₁₋₆alkyl;
 or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 wherein X-R¹ is hydrogen.

10

3. A compound according to any one of the preceding claims wherein A represents a fused membered ring optionally containing up to two heteroatoms selected from O, S and NR⁵, wherein R⁵ is hydrogen or C₁₋₆alkyl, which ring is optionally substituted by up to 2 substituents selected from halogen, C₁₋₆alkyl, hydroxy, C₁₋₆alkoxy or keto.

15

4. A compound as claimed in any one of the preceding claims wherein R² and R³ independently represent hydrogen, C₁₋₆alkyl, aryl, heteroarylC₁₋₆alkyl, heterocyclyl, heterocyclylC₁₋₆alkyl, any of which except hydrogen can be optionally substituted or R² and R³ together with the nitrogen atom to which they are attached form an optionally substituted
20 or 6 membered monocyclic or bicyclic ring.

5. A compound as described in the Examples.

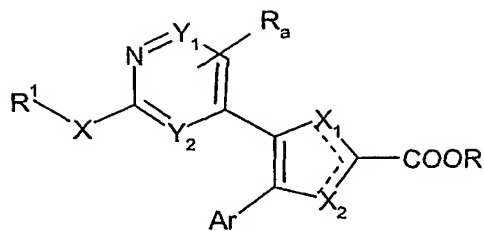
6. A pharmaceutical composition comprising a compound according to any one of claims
25 1 to 5 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

7. The use of a compound according to any one of claims 1 to 5 or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the prophylactic or therapeutic treatment of any disease state in a human, or other mammal, which is exacerbated or caused
30 by a neurotraumatic event.

8. The use of a compound according to any one of claims 1 to 5 or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the prophylactic or therapeutic treatment of cancer.

35

9. A compound of formula (II):



(II)

wherein X , Y_1 , Y_2 , R^1 , R_a , Ar , X_1 and X_2 are as defined for formula (I) and R is hydrogen, C_{1-6} alkyl or aryl C_{1-6} alkyl.

5

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D401/04 A61K31/44 A61P25/00 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 97 12876 A (MERCK & CO INC ;SELNICK HAROLD G (US); CLAREMON DAVID A (US); LIVE) 10 April 1997 (1997-04-10) page 1-3; claim 1	1-9
A	GB 2 306 108 A (MERCK & CO INC) 30 April 1997 (1997-04-30) page 1-3; claim 1	1-9

☐ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
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Date of the actual completion of the international search

1 August 2002

Date of mailing of the international search report

07/08/2002

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INTERNATIONAL SEARCH REPORT

Information on patent family members

PCT/GB 02/02353

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